PATENT SPECIFICATION (11) 1 268 243

1 268 243

NO DRAWINGS

(21) Application No. 12844/69 (22) Filed 11 March 1969

(31) Convention Application No. 711 897 (32) Filed 11 March 1968 in

(33) United States of America (US)

(45) Complete Specification published 22 March 1972

(51) International Classification C 07 d 41/00; A 61 k 27/00

(52) Index at acceptance

C2C 179—271—281 1E4K3 1E4K6 213 220 227 22Y 246 247 250 251 25Y 290 29X 29Y 305 30Y 314 31Y 321 322 323 326 32Y 332 337 342 34Y 351 352 355 360 362 364 365 366 367 36Y 385 396 3A10E3D4 3A12A4A 3A12A4B 3A12B3 3A12B7 3A12C3 3A12C5 3A12C6 3A13B3 3A13C10D 3A13C10F 3A13C10H 3A13C1B 3A13C1C 3A13C4C 3A13C6A 3A13C9 3A13D 3A7V1A4 3A7V1E1 3A7V1G2 3A7V1J1 3A7V2A4 3A7V2E1 3A7V2G2 3A7V2J1 3A7V2K3B 3A7V3A2 3A7V3F1 3A7V3J5 3A8A4 3A8B2 3A8C3 3A8G1 3A8K 43X 45X 45Y 509 50Y 510 51X 534 601 610 613 615 620 621 623 624 625 62X 650 656 660 661 662 670 672 675 680 681 682 699 760 775 776 790 79Y KP LF LH LM MB MM NJ QL QS SG ZH

(54) 1,2,4,5-TETRAHYDRO-3H,3-BENZAZEPINES

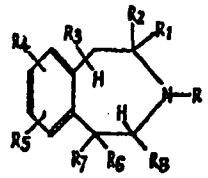
(71) We, WALLACE & TIERNAN INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 91 South Harrison Street, City of East Orange, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to substituted 1,2,4,5-tetrahydro-3H,3-benzazepines.

The compounds of this invention are useful as agents for producing analgesia and thus relieving pain in animals. They are also useful as antagonists of narcotics such as morphine.

As used throughout the following description and claims, the term "lower" means a group containing from 1 to 5 carbon atoms.

According to the present invention there is provided a compound of the formula:

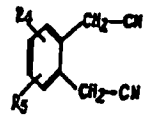


Formula I

or the pharmaceutically acceptable addition salts thereof, wherein R is H, lower alkyl; dialkylamino-alkyl, lower alkenyl containing 3—6 carbon atoms: aryl-C_5—C_6 alkenyl; cycloalkyl-alkyl, for example 2-(1-adamantyl)-ethyl-(adamantyl moiety unsubstituted or substituted with NH_2, OH, OCH_3, halogen, alkyl); aryl-cycloalkyl-alkyl, propargyl; aryl-lower alkyl, the aryl group selected from phenyl, tolyl, nitrophenyl aminophenyl, acylaminophenyl, methoxyphenyl, hydroxyphenyl, methylaminophenyl, ethylaminophenyl, or dimethylaminophenyl; a lower alkyl ester of hydroxyalkyl: a heterocyclic group, an alkyl group substituted by a heterocyclic ring (unsubstituted or substituted with one or more phenyl, hydroxyl or acyl groups), 2-phthalimidoethyl-(the phenyl moiety unsubstituted of substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-(2-isoindolinyl)-ethyl-(the phenyl moiety unsubstituted or

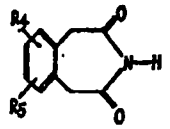
substituted in any of the remaining positions with NH_2, OH, OCH_3, halogen, alkyl); 2-[4-benzyl-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o*, *m*, *or p*-position with NH_2, OH, OCH_3); 2-(4-phenyl-1-piperazinyl)-ethyl -(the phenyl moiety unsubstituted or substituted in the *o*, *m*, *p*-position with NH_2, OH, OCH_3, halogen, alkyl); 2-[4-(*o*-methylbenzyl)-1-piperazinyl]-ethyl-(the phenyl moiety unsubstituted or substituted in the *o*, *m*, or *p*-position with NH_2, OH, OCH_3, halogen, alkyl): R^1 is hydrogen and R^2 is hydrogen, lower alkyl, phenyl or phenyl-lower alkyl, or R^1 and R^2 are lower alkyl; R^3 is hydrogen or lower alkyl; R^4 and R^5 are hydrogen, lower alkoxy, CH_2OCH_2O—, hydroxy, pyridine carboxylic acid ester of hydroxy group, amino, lower alkyl, halogen or nitro; R^6 and R^7 are hydrogen, lower alkyl, phenyl or phenylalkyl; R^8 is hydrogen, lower alkyl, phenyl or phenylalkyl; provided that when R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are hydrogen and R is allyl, dialkylaminoalkyl or unsubstituted heterocyclyl-alkyl, R^4 is hydroxyl; provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 is other than hydrogen when R is either hydrogen, lower alkyl, allyl or phenyl-lower alkyl; and that neither R^4 nor R^5 is 6-chloro when R, R^1, R^2, R^3, R^6, R^7, and R^8 are hydrogen and provided that when R^4 and R^5 are methoxy, R is not hydrogen or methoxy.

In the following discussion of the process of the invention the symbols R through R^8 are to be regarded as defined as above unless there is a specific indication to the contrary in the discussion. The compounds of the invention wherein R is hydrogen may be prepared by treating a compound of the formula



Formula II

with a hydrogen halide in a polar solvent such as acetic acid, warming the resulting 2-amino-4-halobenzazepine with water to provide a cyclic imide of the formula



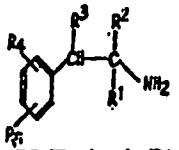
Formula III

and selectively reducing the carbonyl groups adjacent the imido group in the compound of Formula III.

Borane is a suitable reagent for use in reducing the carbonyl groups of the compound of Formula III.

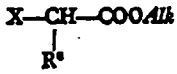
The compounds of the invention wherein R is hydrogen may also be prepared by hydrogenating a compound of Formula II. The hydrogenation is preferably effected catalytically using Raney nickel catalyst.

The compounds of the invention wherein R is hydrogen and any of the substituents R^1 through R^7 are lower alkyl, phenyl or phenyl lower alkyl may be prepared by reacting an amine of the formula



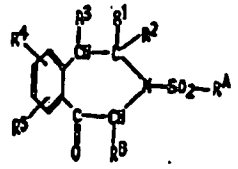
Formula IV

with a compound of the formula R^4—SO_2X wherein R^4 is an organic radical and X is halogen, reacting the corresponding sulfonamide thus obtained with an ester of the formula



Formula V

wherein *Alk* is a hydrocarbon group and X is halogen, hydrolyzing the resulting ester, treating the acid thus obtained with a halogenating agent such as sulfonyl chloride to provide the corresponding acid halide, adding the acid halide to a cold suspension of aluminum trihalide to provide a benzazepinone of the formula



Formula VI

selectively reducing the carbonyl group in the azepinone moiety of the compound of Formula VI and splitting off the radical $R^A—SO_2—$ therefrom.

p-Toluenesulfonyl chloride is prepared for use as the compound of the formula $R^A—SO_2X$ while ethylbromoacetate or appropriately substituted derivative thereof is preferred as the ester of Formula V.

Sodium borohydride is a preferred reagent for use in reducing selectively the carbonyl group in the compound of Formula VI.

The compounds of Formula I wherein R is other than hydrogen may be prepared by reacting such a compound in which R is hydrogen with a reagent which will replace the hydrogen with one of groups R other than hydrogen. Such reagents include compounds of the formulas RX and R—C:OX wherein R is other than hydrogen and X is halogen, as well as aldehydes and ketones having at least three carbon atoms.

When a reagent of formula R—C:OX is used the carbonyl moiety is subsequently selective reduced to a methylene group. Lithium aluminum hydride is a preferred reagent for the reduction.

When an aldehyde of ketone is used as the reagent the double bond in the moiety attached to the nitrogen atom in the azepine ring of the product may be reduced. Sodium borohydride is preferred for the reduction.

Suitable changes can be made in the substituents R^4 and R^5 in compounds of Formula I by means apparent to those skilled in the art. In one embodiment of the process of the invention, compounds of Formula I wherein R is hydrogen and at least one of R^4 and R^5 is an alkoxy group, are treated with aqueous hydrogen halide, preferably the bromide, to cleave the alkoxy group and provide a corresponding hydroxy group. The cleavage may be effected before or after the reaction of the compound of Formula I with compounds of formulas RX and RC:OX or an aldehyde or a ketone as discussed above.

Being organic bases the above compounds readily form salts with organic or inorganic acids such as hydrochloric, maleic, tartaric, sulfuric, and other nontoxic acids to form pharmaceutically acceptable acid addition salts.

Particularly satisfactory compounds from the point of view of analgesia and narcotic antagonism are compounds in which R^4 and R^5 are hydroxy or lower alkoxy.

The following Reaction Scheme A illustrates graphically two general techniques for preparing a representative compound of Formula I wherein R is a hydrogen atom, one of R^4 and R^5 is a methoxy group and the other a hydrogen atom, substituents R^1 to R^3 and R^6 to R^8 being hydrogen.